OIPE JC148
MAY 17 2004
PATENT & TRADEMARK OFFICE

IFW

Application No.: 10/810,005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

DANA P. GADDY

Serial No.: 10/810,005

Filed: March 26, 2004

For: METHOD FOR DIAGNOSIS AND TREATMENT OF BONE TURNOVER

Attorney Docket No.: 022438.45889

TRANSMITTAL LETTER

Mail Stop: DD
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The following documents for the above-captioned application are enclosed herewith:

1. Information Disclosure Statement;
2. Information Disclosure Citation (PTO-1449); and
3. Return Postcard.

If a fee is due, please debit Deposit Account No. 50-0858. In this regard, a duplicate copy of this Transmittal Letter is enclosed herewith.

Respectfully Submitted,

Butler, Snow, O'Mara, Stevens & Cannada, PLLC

May 13, 2004
Date

By: Susan B Fentress
SUSAN B. FENTRESS
Reg. No. 31,327
6075 Poplar Avenue, Suite 500
Memphis, TN 38119
(901) 680-7319

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INFORMATION DISCLOSURE STATEMENT

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Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached Form PTS-A820. A copy of each of the references listed on the attached form is submitted herewith.

Applicant respectfully requests that the Examiner consider the listed documents and indicate that it was considered by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed documents are material or constitute "prior art". If the Examiner applies the document as prior art against any claim in the application and Applicant determines that the cited documents do not constitute "prior art" under United States law. Applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicant further reserves the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the documents be applied against the claims of the present application.

Document AA – D. Gaddy-Kurten, et al. "Inhibin Suppresses and Activin Stimulates Osteoblastogenesis and Osteoclastogenesis in Murine Bone Marrow Cultures" shows that inhibin suppresses osteoblastogenesis and osteoclastogenesis in bone marrow cell cultures.

Document BB – Wiater, et al. "Inhibin is an Antagonist of Bone Morphogenetic Protein Signaling" discloses that inhibin is an antagonist of bone morphogenetic protein signaling of gonadal origin.

Document CC – Shintani, et al. "Potent induction of activin A secretion from monocytes and bone marrow stromal fibroblasts by cognate interaction with activated T cells" discloses activin A is a multifunctional cytokine essential for cell differentiation and apoptosis including erythroid cell differentiation in the bone marrow. In addition, activin A is induced by inflammation and exerts anti-inflammatory effects. However, the mechanism of activin A induction is still unclear, especially by inflammatory processes. Here we show that activin A secretion from monocytes and bone marrow stromal fibroblasts, its major sources in the bone marrow, is markedly enhanced by cognate interaction with activated T cells. This process is mediated by CD40/CD40 ligand interaction as well as concomitantly secreted T cell-derived cytokines, granulocyte macrophase-colony stimulating factor, and interferon-gamma. Furthermore, stromal fibroblasts as well as monocytes provide a costimulatory signal to anti-CD3-treated T cells via CD80 and CD86 to maintain the enhanced activin A production. These findings suggest that activin A is potently induced in the bone marrow and may play a role in the suppression of inflammatory or immune processes.

Document DD – Ebeling, et al. "Bone turnover markers and bone density across the menopausal transition." We measured lunbar spine and femoral neck bone mineral density (BMD); urine markers of bone resorption; serum markers of bone formation; and serum gonadotrophin, estradiol and inhibin concentrations in a population-based cohort of 281 women aged 45-57 yr. Women were classified into pre-, peri-, and postmenopausal groups, depending on menstrual bleeding patterns. Compared with premenopausal women, BMD was lower only in postmenopausal women but not in women currently using hormone replacement therapy (HRT). BMD decreased with age in the perimenopausal group. Compared with premenopausal women, perimenopausal women had 20% greater urine N-telopeptide excretion ($P < 0.05$) and a doubling

of gonadotrophin levels ($P < 0.01$), whereas serum estradiol and bone formation marker concentrations were no different. Postmenopausal Women had greater levels of bone turnover markers ($P < 0.0001$), except free deoxypyridinoline and type I procollagen propeptide. Among postmenopausal women, bone resorption markers were lower in those using HRT. Levels of nearly all bone turnover markers were positively related to serum FSH concentrations ($P < 0.0001$). Overall, the major independent predictors of BMD were age, urine N-telopeptide, serum bone alkaline phosphatase, and serum, FSH, whereas urine free deoxypyridinoline was positively related to BMD in pre- and perimenopausal women. In conclusion, the perimenopause is associated with elevated bone resorption rates and declining BMD, and factors in addition to estrogen deficiency may also contribute to the pathogenesis of postmenopausal osteoporosis.

Document EE – Hirotani, et al. "Activin A increases the bone mass of grafted bone in C3H/HeJ mice" discloses Activin A, a member of the TGF-b superfamily, is abundant in bone matrix, but little is known about its physiological role in bone metabolism. The present study was undertaken to determine whether topical activin A can increase the bone mass of isografted bone. The tibiae were bilaterally dissected from a donor C3H/HeJ mouse and transplanted subcutaneously in the dorsal region of a recipient mouse. One isografted tibia was topically infused for either 1, 2, 3, or 4 weeks with activin A, using an osmotic minipump at a dose of 0.02, 0.2, or 2 ng/hr. The other tibia was infused with 0.9% NaCl (control). The following results were obtained: (1) Topical activin A (2 ng/hr) stimulated periosteal bone formation after 2 or 3 weeks. The bone area in a standardized transverse section averaged 1.3 fold that in the control. (2) Numerous cuboidal or conical osteoblasts appeared on the surface of newly formed bone after the infusion of activin A for 2 or 3 weeks. Autoradiographic studies using 3H-proline revealed that the surface area of newly formed bone labelled with autoradiographic silver grains was greater in activin A-treated bone than in the control, suggesting an increased synthesis and secretion of collagen by osteoblasts. (3) Topical activin A increased the number of osteoclasts after 2 to 4 weeks. Furthermore, enhanced or increased bone resorption was observed in the projected anterior site of activin A-treated bone after 4 weeks. These results suggest that topical activin A increases the bone mass of isografted bone by increasing bone turnover.

Document FF – U.S. Patent Application No.: 2003/0015208 discloses methods of

diagnosing and preventing bone loss and/or enhancing bone formation are disclosed. The invention additionally provides methods of diagnosing a predisposition to bone loss. The methods mathematically combine the information provided by imaging tests with the information provided by biomarkers to provide an index value. The index value is used for diagnosis of bone diseases, and to assess the progress of treatment of bone diseases.

Document GG – U.S. Patent No.: 6,489,445 discloses compositions and methods for increasing bone density using antibodies directed to a novel class or family human of TGF-.beta. binding proteins are disclosed. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases associated with a loss of bone density, for example osteoporosis. The disclosed compositions include polypeptides, and their encoding polynucleotides, which specifically bind to at least one human bone morphogenic protein (BMP) selected from BMP-5 and BMP-6air.

Document HH – U.S. Patent No.: 5,952,182 discloses elevated levels of Inhibin-A in maternal serum or plasma have been shown to indicate the presence of Down's Syndrome. The assay method comprises the use of a monoclonal antibody specific for at least part of the inhibin-A .beta. sub-unit (.beta.A), and another monoclonal antibody specific for at least part of the Inhibin-A .alpha. sub-unit. The .beta.A antibody is used to capture Inhibin-A from the test sample, and the .alpha. sub-unit antibody is used as the detection antibody and is linked to a detectable marker. The method is carried out in the first or second trimester as a screening test to select patients for subsequent diagnostic testing.

Document II – U.S. Patent No.: 5,830,671 discloses a method for assaying for the presence of a substance that modulates a cytokine of the TGF.beta. superfamily. A substance which is suspected of modulating a cytokine of the TGF.beta. superfamily and a TGF.beta. binding compound which is not a TGF.beta. receptor and which contains a TRH1 domain, or a portion or mimetic thereof, is reacted with a cytokine of the TGF.beta. superfamily under conditions where the compound, portion or mimetic thereof, and the cytokine are capable of forming a complex. Complexes, free compound and/or cytokine are assayed and compared with a control. The invention also relates to a composition comprising at least one compound which is not a TGF.beta. receptor and which contains the TRH1 domain or a portion, or a mimetic

thereof, and a pharmaceutically acceptable carrier, auxiliary or excipient and to methods of treatment using the composition. Further the invention relates to a method of enhancing the activity of growth factors.

Document JJ – International Application No. WO 87/05702 discloses a method of immunoassay for the estimation of inhibin in an inhibin-containing sample which comprises the step of using an antibody directed against inhibin. Preferably, the antibody is contained in an antiserum raised by injecting an animal with an antigen selected from the group consisting of naturally-occurring or recombinant inhibin, or sub-units, fragments or derivatives thereof. The assay may suitably be a radioimmunoassay, a fluorescence-based immunoassay, or an enzyme-linked immunosorbent assay using labeled 58kD or 31kD inhibin as tracer. Tracers and standards for use in the assay are described and claimed.

Document KK – N.A. Klein, et al. "Decreased Inhibin B Secretion is Associated with the Monotropic FSH Rise in Older, Ovulatory Women: A Study of Serum and Follicular Fluid Levels of Dimeric Inhibin A and B in Spontaneous Menstrual Cycles." This study sought to compare circulating and follicular fluid (FF) concentrations of dimeric inhibin A and B utilizing specific two-site ELISAs for these hormones in normal older and younger ovulatory women. METHODS. Normally ovulating women age 40-45 (n = 10) and 20-25 (n = 13) were studied throughout the follicular phase with daily blood sampling, transvaginal ultrasound examinations, and dominant follicle aspiration. When the dominant follicle reached a mean diameter of 16 mm or serum estradiol (E2) was > or = 550 pmol/L, 10,000 IU of hCG was administered intramuscularly followed 32 hours later by transvaginal follicle aspiration. Serum and FF samples were analyzed for E2, FSH, and inhibin A and B. Daily hormone levels were compared by ANOVA, and mean results were compared using t-tests. RESULTS :Older women developed a dominant follicle sooner, meeting criteria for hCG cycle day 10.6 +/- 0.4 vs. 14.5 +/- 1.0 p < 0.001. As expected, the older group had higher maximal serum FSH concentrations compared to the younger women (11.4 +/- 0.5 vs. 8.0 +/- 0.4 IU/L, p < 0.001). We compared hormone concentrations from days-1 to 3 (where day 0 = day of maximal FSH concentration). E2 concentration was higher in the older women (p = 0.002), and there was no significant difference in inhibin A secretion (p = 0.61). In contrast, mean inhibin B concentration was significantly lower in the older women (p = 0.04). On the day of aspiration of the dominant follicle, serum

inhibin B was decreased in the older subjects (42.6 +/- 6.5 vs. 153.1 +/- 53 pg/ml, p = 0.02), whereas older subjects had higher levels of inhibin A (106 +/- 16 vs. 60.4 +/- 9.4 pg/ml, p = 0.04) and similar E2 levels (665 +/- 35.2 vs. 687 +/- 92 pmol/L, p = 0.83). There were no differences in FF concentrations of inhibin B (164 +/- 31 vs. 174 +/- 37 ng/ml, p = 0.85), inhibin A (317.7 +/- 38 vs. 248 +/- 57 ng/ml, p = 0.16), or E2 (2074 +/- 294 vs. 2474 +/- 338 nmol/L, p = 0.82) in the older and younger women. CONCLUSION. Follicular phase inhibin B secretion is decreased in older ovulatory women who demonstrate a monotropic FSH rise, whereas inhibin A secretion is similar to that in younger women. The dominant follicle in these older women appears to be normal in terms of FF E2 and inhibin content. We speculate that decreased inhibin B secretion most likely reflects a diminished follicular pool in older women and may be an important regulator of the monotropic FSH rise.

Document LL – Peter R. Ebeling, et al. "Bone Turnover Markers and Bone Density Across the Menopausal Transition". We measured lunbar spine and femoral neck bone mineral density (BMD); urine markers of bone resorption; serum markers of bone formation; and serum gonadotrophin, estradiol and inhibin concentrations in a population-based cohort of 281 women aged 45-57 yr. Women were classified into pre-, peri-, and postmenopausal groups, depending on menstrual bleeding patterns. Compared with premenopausal women, BMD was lower only in postmenopausal women but not in women currently using hormone replacement therapy (HRT). BMD decreased with age in the perimenopausal group. Compared with premenopausal women, perimenopausal women had 20% greater urine N-telopeptide excretion (P < 0.05) and a doubling of gonadotrophin levels (P < 0.01), whereas serum estradiol and bone formation marker concentrations were no different. Postmenopausal Women had greater levels of bone turnover markers (P < 0.0001), except free deoxypyridinoline and type I procollagen propeptide. Among postmenopausal women, bone resorption markers were lower in those using HRT. Levels of nearly all bone turnover markers were positively related to serum FSH concentrations (P < 0.0001). Overall, the major independent predictors of BMD were age, urine N- telopeptide, serum bone alkaline phosphatase, and serum, FSH, whereas urine free deoxypyridinoline was positively related to BMD in pre- and perimenopausal women. In conclusion, the perimenopause is associated with elevated bone resorption rates and declining BMD, and factors in addition to estrogen deficiency may also contribute to the pathogenesis of postmenopausal osteoporosis.

Document MM – N.P. Groome, et al. "Detection of dimeric inhibin throughout the human menstrual cycle by two-site enzyme immunoassay".

Document NN – Wylie Vale, et al. "Reproductive and Other Roles of Inhibins and Activins".

Document OO – John Yu, et al. "Importance of FSH-releasing protein and inhibin in erythrodifferentiation".

Document PP – Koji Fujimoto, et al. "Purification of Megakaryocyte Differentiation Activity from A Human Fibrous Histiocytoma Cell Line: N-Terminal Sequence Homology with Activin A".

Document QQ – Hal E. Broxmeyer, et al. "Selective and indirect modulation of human multipotential and erythroid hematopoietic progenitor cell proliferation by recombinant human activin and inhibin".

Document RR – Andrew W. Yu, et al. "Detection of Functional and Dimeric Activin A in Human Marrow Microenvironment".

Document SS – L.F. Bonewald, et al. "Role of Transforming Growth Factor-Beta in Bone Remodeling".

Document TT – John M. Wozney "The Bone Morphogenetic Protein Family and Osteogenesis".

Document UU – Yasushi Ogawa, et al. "Bovine Bone Activin Enhances Bone Morphogenetic Protein-induced Ectopic Bone Formation".

Document VV – Masayuki Funaba, et al. "Follistatin and Activin in Bone: Expression and Localization during Endochondral Bone Development".

Document WW – S. Inour, et al. "Localization of Follistatin, an Activin-Binding Protein, in Bone Tissues".

Document XX – Y. Oue, et al. "Effect of Local Injection of Activin A on Bone

Formation in Newborn Rats".

Document YY – Helene Meunier, et al. "Gonadal and extragonadal expression of inhibin α, βA, and βB subunits in various tissues predicts diverse functions".

Document ZZ – Peter R. Ebeling, et al. "Bone Turnover Markers and Bone Density Across the Menopausal Transition".

Document AB – S. Muttukrishna, et al. "Serum concentrations of dimeric inhibin during the spontaneous human menstrual cycle and after treatment with exogenous gonadotrophin".

Document AC – Frances Haynes, et al. "Differential Control of Gonadotropin Secretion in the Human: Endocrine Role of Inhibin".

In the event the Examiner has any questions regarding this document, please contact the undersigned at the telephone number listed below.

Respectfully Submitted,

Butler, Snow, O'Mara, Stevens & Cannada, PLLC

May 13, 2004
Date

By: Susan B. Fentress
SUSAN B. FENTRESS
Reg. No. 31,327
6075 Poplar Avenue, Suite 500
Memphis, TN 38119
(901) 680-7319

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, on 5-13-04 in an envelope addressed to: Mail Stop: DD, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Lori L. Wood
LORI L. WOOD

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Docket Number (Optional) 022438.45889	Application Number 10/810,005
	Applicant(s) Dana Gaddy	
	Filing Date March 26, 2004	Group Art Unit

OIPE
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U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	FF	2003/0015208	01/23/03	Lang, et al.	128/922	600/562	05/28/02
	GG	6,489,445	12/03/02	Brunkow, et al.	530/350	530/300	09/21/00
	HH	5,952,182	09/14/99	Groome, et al.	435/7.1	435/7.94	05/22/95
	II	5,830,671	11/03/98	Dennis, et al.	435/7.8	435/4	05/12/97

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation YES	Translation NO
	JJ	WO 87/05702	09/24/87	AU	33/541	33/74	✓	

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

	AA	D. Gaddy-Kurten, et al. "Inhibin Suppresses and Activin Stimulates Osteoblastogenesis and Osteoclastogenesis in Murine Bone Marrow Cultures" 2002
	BB	Wiater, et al. "Inhibin is an Antagonist of Bone Morphogenetic Protein Signaling" December 18, 2002

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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*EXAMINER INITIAL		OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)
	CC	Shintani, et al. "Potent induction of activin A secretion from monocytes and bone marrow stromal fibroblasts by cognate interaction with activated T cells" 2002
	DD	Ebeling, et al. "Bone turnover markers and bone density across the menopausal transition" 1996
	EE	Hirotani, et al. "Activin A increases the bone mass of grafted bone in C3H/HeJ mice" 2002
	KK	N.A. Klein, et al. "Decreased Inhibin B Secretion is Associated with the Monotropic FSH Rise in Older, Ovulatory Women: A Study of Serum and Follicular Fluid Levels of Dimeric Inhibin A and B in Spontaneous Menstrual Cycles" 1996
	LL	Peter R. Ebeling, et al. "Bone Turnover Markers and Bone Density Across the Menopausal Transition" 1996
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	NN	Wylie Vale, et al. "Reproductive and Other Roles of Inhibins and Activins" 1994
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	PP	Koji Fujimoto, et al. "Purification of Megakaryocyte Differentiation Activity from A Human Fibrous Histiocytoma Cell Line: N-Terminal Sequence Homology with Activin A" 1991
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P09B/REV04

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